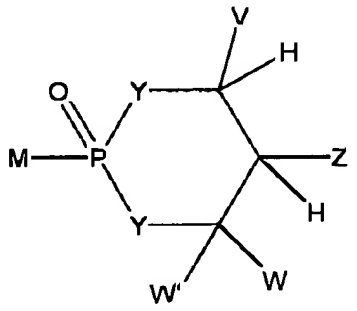
AMENDMENT

In the Claims

Please add the new claim as follows:

158. A method of treating diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product by administering to an animal in need thereof a pharmaceutically effective amount of a compound of formula I:



I

wherein:

V, W, and W′ are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W′ are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-HR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, SCO_2R^3, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W′ are not all -H;

b) when Z is $-R^2$ or $-OR^2$, then V is not -H, alkyl, aralkyl, or alicyclic;

c) when Z is CHR^2OH, then M is not –NH(lower alkyl), –N(lower alkyl)$_2$, –NH(lower alkylhalide), –N(lower alkylhalide)$_2$ or –N(lower alkyl)(lower alkylhalide); and

d) when V is aryl or substituted aryl, then M is not –O(D) where D is hydrogen, a metal ion or an ammonium ion;

R^2 is selected from the group of R^3 and -H;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R^{12} is selected from the group of -H, and lower acyl;

each Y is independently selected from the group of -O-, and $-NR^6-$;

M is selected from the group of drugs MH containing an –OH, $-NHR^2$, or -SH group, and that is attached to the phosphorus in formula I via O, N or S of said OH, $-NHR^2$, or -SH group;

and pharmaceutically acceptable prodrugs and salts thereof.

The addition of this claim adds no new matter to the application. Support can be found throughout the specification, for instance at p. 2, lines 15-21.

THE RESTRICTION REQUIREMENT

The Examiner has required restriction to one of the following Groups:

I. Claims 1-33, drawn to phosphorous cyclic prodrug compounds of formula I, classified in class 558, subclass 73.

II. Claims 134-157, drawn to phosphorous cyclic prodrug compounds of formula VIII, classified in class 558, subclass 74.

Group I is hereby elected, with traverse. Withdrawal of the Restriction Requirement is requested.

The Examiner contends that the inventions of Groups I and II are related by combination and subcombination, where "the combination as claimed does not require the particulars of the subcombination as claimed because the combination of the V and W variable to form an additional ring is a species within the genus of formula I." Office Action p. 2. Furthermore, the Examiner argues that the subcombination has a separate utility as a prodrug, as set forth in Group II.

The Applicants believe that the Examiner meant to have Group I include Claims 1-133 and not 1-33, since Claims 1-133 are all drawn to phosphorous cyclic prodrug compounds of Formula I. The Applicants also note that Claims 155-157 are likewise drawn to phosphorous cyclic prodrug compounds of Formula I. Therefore, the Applicants respectfully request clarification of the claims comprising Groups I and II.

According to MPEP § 803, two criteria are required for proper restriction: 1) that the inventions be independent or distinct; and 2) that there be a serious burden on the examiner. The Applicants believe that the Examiner has not met either criteria.

First, the Applicants believe that the inventions are not independent or distinct. The Applicants believe that Groups I and II are not related as a combination and subcombination, because Claim 1 does not contain any additional elements not present in Claim 134. Even the Examiner admits that Group II (Formula VIII) compounds are a species within the genus of Group I (Formula I) compounds.

Second, the Applicants believe that there would not be an undue burden on the Examiner to search both groups together. The Examiner admits that Group II (Formula VIII) compounds are a species within the genus of Group I (Formula I) compounds. Therefore a search of Group I compounds would necessarily turn up prior art on Group II compounds.

THE ELECTION OF SPECIES REQUIREMENT

The Examiner further requires that the Applicants elect a single disclosed species for the drugs MH. The Applicants are further advised to include an identification of the species elected and a listing of all claims readable thereon.

The Applicants hereby elect the species etoposide, with traverse. The claims from Group I reading thereon are 1-49, 65-88, 104-118, 155-157.

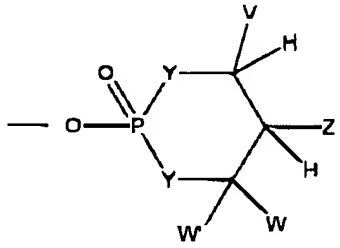
The Examiner argues that the "definition for the variable MH represents a multiplicity of patentably distinct species." Office Action p. 3. The Examiner requests that Applicants select a single species from those set forth in claim 5 or claim 67.

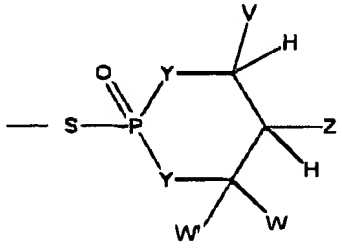
The Examiner appears to be requiring election of a single compound in claim 5 or 67. However, the Applicants draw the Examiner's attention to the fact that within claim 5 or claim 67 several of the compounds are part of the same group. For instance, etoposide, teniposide, NK-611, GL-331, and azatoxin all belong to the class epipodophyllotoxin.

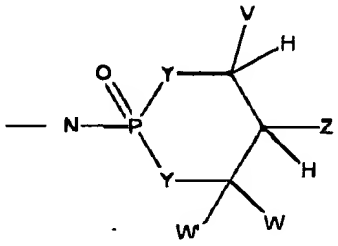
More importantly, the Applicants note that the invention is broader than any particular MH group. The invention is directed toward novel prodrugs. The Applicants have recognized

the ability to modify known drugs and create prodrug technology for them. Therefore, the invention is not limited to the structural identity of the MH group. MH is merely a variable.

Applicants submit that it would make more sense to base the search on the type of atom attached to the P, for instance the O, N, or S of the -OH, -NHR^2, or -SH groups.







Applicants believe that a restriction based upon the above searches would make more sense than a restriction based on each MH group.

For the foregoing reasons, the Applicants respectfully request the Withdrawal of the Restriction Requirement and Election of Species Requirement.

Respectfully Submitted,

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